Novel generation influenza vaccines: Adjuvants for increasing pandemic vaccine supply

2nd WHO Consultation on a Global Action Plan for pandemic Influenza vaccines
Geneva 13th July 2011
Pandemic influenza vaccines

- Key issues -

- Response time
  (currently ~6 months)

- Production capacity
  (currently ~1000 million doses trivalent vaccine world-wide)

- Efficacy/Safety
  (human trials with prototype H5, H9 vaccines)

NB: Regulatory issues
<table>
<thead>
<tr>
<th>Animal species</th>
<th>H5N1 strain</th>
<th>Clinical signs postinfection</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>Multiple</td>
<td>Weight loss, lethargy, ruffled fur, breathing difficulties and death</td>
<td>[33,38,39]</td>
</tr>
<tr>
<td>(laboratory strains)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>A/chicken/HK/220/97</td>
<td>n.d.</td>
<td>[131]</td>
</tr>
<tr>
<td>Rat</td>
<td>A/chicken/HK/220/97</td>
<td>n.d.</td>
<td>[131]</td>
</tr>
<tr>
<td>Ferret</td>
<td>Multiple</td>
<td>Fever, severe respiratory symptoms, neurologic signs and death</td>
<td>[65,67]</td>
</tr>
<tr>
<td>Cat</td>
<td>A/VN/1194/04</td>
<td>Nasal discharge, icterus, neurologic signs and death</td>
<td>[55,56]</td>
</tr>
<tr>
<td>Dog</td>
<td>A/chicken/GxLA/1204/2004</td>
<td>n.d.</td>
<td>[132]</td>
</tr>
<tr>
<td>Cynomolgus macaque</td>
<td>Multiple</td>
<td>Fever and severe respiratory failure</td>
<td>[74,78]</td>
</tr>
<tr>
<td>Pig</td>
<td>Multiple</td>
<td>Mild cough, fever and anorexia</td>
<td>[54,133,134]</td>
</tr>
<tr>
<td>Red fox</td>
<td>A/whooper swan/Germany/R65-1/2006</td>
<td>Rise in body temperature in two out of three foxes</td>
<td>[135]</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>A/Thailand/16/04</td>
<td>Modest weight loss Bronchointerstitial pneumonia</td>
<td>[48]</td>
</tr>
<tr>
<td></td>
<td>A/Vietnam/1203/04</td>
<td></td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td>Rec A/VN/1203/04</td>
<td>n.d.</td>
<td>[50]</td>
</tr>
<tr>
<td>Cattle</td>
<td>A/cat/Germany/R606/2006</td>
<td>n.d.</td>
<td>[136]</td>
</tr>
</tbody>
</table>

n.d.: Not detected.

DIAGNOSTIC READ-OUTS

Clinical & Virological Parameters

Seasonal H1N1  pH1N1 2009  HPAI H5N1

Temperature  Virus Load

Munster et al., Science 2009
Del Giudice et al., Science TM 2009
Chutinimitkul et al., J.Virol 2010
Herfst et al., Vet.Pathol. 2010
Bosch et al., J.Virol. 2010
Kreijtz et al., J.Gen.Virol. 2010
v.d.Brand et al., JID 2010
v.d.Brand et al., J.Virol 2010
Pandemic influenza vaccines

- Room for improvement -

Strain selection

Seed-strain preparation

Production systems

“small” changes; easy to incorporate

New targets; identify correlates of protection

Improve efficacy: adjuvants & delivery systems

larger changes; long path before implementation?
Adjuvants and antigen presentation systems for viral vaccines tested in humans (1/2)
(an arbitrary selection)

<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>Viral antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mineral salts</strong></td>
<td>numerous</td>
</tr>
<tr>
<td>Aluminium salts</td>
<td>HBsAg, HSV (gD)</td>
</tr>
<tr>
<td>Alum + MPL</td>
<td></td>
</tr>
<tr>
<td><strong>Emulsions</strong></td>
<td></td>
</tr>
<tr>
<td>MF 59 / ASOx</td>
<td>Flu</td>
</tr>
<tr>
<td></td>
<td>HBV (rPreS2-S)</td>
</tr>
<tr>
<td></td>
<td>HSV2 (rgB + rgD)</td>
</tr>
<tr>
<td></td>
<td>HIV1 (gp 120)</td>
</tr>
<tr>
<td></td>
<td>CMV (rgB)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
</tr>
<tr>
<td></td>
<td>Flu (split)</td>
</tr>
<tr>
<td></td>
<td>HIV1</td>
</tr>
<tr>
<td>MF59 + MTP-PE</td>
<td>HIV1 (gp120)</td>
</tr>
<tr>
<td>QS21</td>
<td>HIV1 (gp120 depleted)</td>
</tr>
<tr>
<td>Incomplete Freund (IFA)</td>
<td>HIV1 (Tat toxoid)</td>
</tr>
<tr>
<td>Montamide ISA51</td>
<td></td>
</tr>
</tbody>
</table>
Adjuvants and antigen presentation systems for viral vaccines tested in humans (2/2) (an arbitrary selection)

**Emulsions (cont.)**
- QS21
- Incomplete Freund (IFA)
- Montamide ISA51
- HIV1 (gp120)
- HIV1 (gp120 depleted)
- HIV1 (Tat toxoid)

**Bacterial products**
- MPL (like)
- Holotoxins (CT, PT, LT)
  - numerous
  - Flu

**Immunoadjuvants**
- Cytokines
  - numerous

**Particulate formulations**
- Liposomes
- Virosomes
- ISCOMS
  - Flu
  - Flu, HAV
  - numerous
Pandemic influenza vaccines
- Improve efficacy; adjuvants & delivery systems -

- Adjuvants & antigen delivery systems
  Aluminum salts
  MF59
  ASO3
  Virosomes
  ISCOMs
  Others....

- Variety of presentations
  Subunits
  Split vaccines
  Whole inactivated virus
  Live-attenuated virus
  Virus-like particles
  Recombinant proteins
  DNA vaccines
  Others....
New adjuvanted influenza vaccines / candidates
(an arbitrary selection)

- **Approved:**
  - MF59 (squalene emulsion) seasonal / pandemic
  - AS03 (squalene/tocopherol emulsion) pandemic
  - Alum pandemic
  - Virosomes (liposomes) seasonal
  - Polyoxidonium (poly-electrolyte) seasonal
- **Clinical studies (phase 1, 2)**
  - Iscom / Iscom Matrix
  - AF3 (squalene o/w emulsions)
  - SE (squalene o/w emulsions)
  - GLA (TLR 4 agonist)
  - Covaccine (TLR 4 agonist)
  - Flagellin (TLR 5 agonist)
  - IC31 (dI:dC – TLR9 agonist)
  - Inulin (complement activator)
  - JVRS-100 (cationic liposome)
Formalin inactivated alum adjuvanted vaccines: an additional risk?

- Formalin-inactivated paramyxovirus vaccines adjuvanted with alum can predispose to hypersensitivity responses (sixties!!!)

- Similar pathology seen for FI–RSV, FI–MV, FI–hMPV, SARS–CoV

- How about formalin inactivated Flu alum vaccines?
Immunopathology study in monkey: General conclusion about safety

- Protection against homologous challenge
- **No pneumonia exacerbation** observed when monkeys vaccinated with an inactivated split-virion influenza A/H5N1 adjuvanted with aluminum hydroxide were challenged with a parental wild type strain

Ruat *et al.*, J.Virol., 2008
Protective immunity
(Rimmelzwaan et al., Vaccine 1998)
MF59-adjuvanted Vaccine was 75-91% More Efficacious Than Non-adjuvanted Influenza Vaccine in All Age Groups: Vaccine-matched Strains

N= 4,707, 2007 – 2009 Seasons

VE(%) compared to non influenza control vaccine

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>6 - &lt;72</th>
<th>6 - &lt;36</th>
<th>36 - &lt;72</th>
<th>6 - &lt;24</th>
</tr>
</thead>
<tbody>
<tr>
<td>45%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative efficacy of Fluad vs. non-adjuvanted vaccine (TM)

<table>
<thead>
<tr>
<th>30%</th>
<th>60%</th>
<th>91%</th>
</tr>
</thead>
<tbody>
<tr>
<td>89%</td>
<td>81%</td>
<td>96%</td>
</tr>
</tbody>
</table>

*Statistically significant.

Lung damage: HPAI H5N1 virus challenge in ferrets
- response to NA important -

Bosch B.J. *et al.*, J.Virol. 2010
### Assessment of pre-pandemic H5N1 clinical trials

<table>
<thead>
<tr>
<th>Type of vaccine</th>
<th>Compliance with EU licensing criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Split vaccine no adjuvant</td>
<td>Need two doses of 90 µg</td>
</tr>
<tr>
<td>Split/subunit vaccine with alum</td>
<td>Need two doses of 30–45 µg</td>
</tr>
<tr>
<td>Whole virus (egg) with alum</td>
<td>Need two doses of 10–15 µg</td>
</tr>
<tr>
<td>Subunit with MF59 adjuvant</td>
<td>Need two doses of 7.5 µg</td>
</tr>
<tr>
<td>Whole virus Vero cell culture, no adjuvant</td>
<td>Need two doses of 7.5 µg</td>
</tr>
<tr>
<td>Split vaccine with AS adjuvant</td>
<td>Need two doses of 3.8 µg</td>
</tr>
</tbody>
</table>

Data presented at WHO meeting, February 2007

(Sanofi Pasteur, 4 Companies in Jp, CSL, Microgen, Sinovac, GSK, Novartis,Baxter)

(Courtesy: John Wood)
The three CHMP criteria are exceeded by all the adjuvanted doses: seroconversion rates
Reactogenicity data are consistent with results obtained in H5N1/AS03\textsubscript{A} pandemic vaccine: general adverse events

H5N1/AS03<sub>A</sub> pandemic vaccine has shown a broad and persistent immune response

Two immunisations at day 1 and day 21 with H5N1 A/Vietnam/1194/04 split virus, AS03<sub>A</sub>

MF59-ADJUVANTED H5N1-VIETNAM VACCINE
GENERATED BROADER ANTIBODY PROFILE COMPARED TO
UNADJUVANTED VACCINE (phage-display library)

STUDY-1:
NIAID (HAI-80)

Correlates of broad protection?

Composition MF59:
0.5% Polysorbate 80
(water–soluble surfactant)
0.5% Sorbitan Triolate
(oil–soluble surfactant)
4.3% Squalene –oil
Water for injection
10 mM Na–citrate buffer

In adults, already primed by natural infection (1), vaccination with plain influenza vaccine essentially expands pre-existing memory B cells directed against the HA2 region, with little effect on priming naive B cells against the HA1 region (2). Vaccination with MF59-adjuvanted vaccine, dramatically primes naive B cells that now produce antibodies against the HA1 region (3).

Khurana et al, Science Transl Med 2011
Ferrets vaccinated with AS-adjuvanted H5N1 split candidate vaccine

- 2 immunisations of ferrets at D0 and D21 (H5N1 A/Vietnam/1194/04 split virus / AS)
- Heterologous challenge (wild-type virus A/Indonesia/5/05, $10^5$ TCID50) at D49
- Post challenge results at D5

<table>
<thead>
<tr>
<th>Group</th>
<th>Dead</th>
<th>Alive</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled controls (15 µg Antigen only or AS only)</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.7 µg H5N1 – AS</td>
<td>1</td>
<td>5</td>
<td>83</td>
</tr>
<tr>
<td>3.8 µg H5N1 – AS</td>
<td>0</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>7.5 µg H5N1 – AS</td>
<td>0</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>15 µg H5N1 – AS</td>
<td>0</td>
<td>6</td>
<td>100</td>
</tr>
</tbody>
</table>

Baras et al., PLoS One 2008
Influenza pandemic virus 2009
- New H1N1 -

New pandemic
- First animal models
  testing vaccines
  testing antivirals
  studying pathogenesis
- First genetic and antigenic data
- Clinical network
  antiviral therapy
  (IV / ICU / ECMO)
  antiviral resistance

Key publications:
J. v.d. Brand et al, JID 2010
S. Herfst et al J.Virol. 2010
F. Wildschut et al. Plos One 2010
G. Del Giudice et al. Science TM 2009
Neutralization assay (Challenge strain)

Neutralizing antibodies observed in all groups immunized with AS03-split H1N1 vaccines → 88% response rate (100% with two doses, 64% with a single dose).
Lower virus load observed in animals immunized with AS03-adjuvanted vaccines compared to ferrets receiving the non-adjuvanted vaccine (or PBS). No virus detected with two doses of AS03-adjuvanted vaccine, virus detected in 27% (3/11 ferrets) ferrets receiving a single dose.
Seasonal vaccine provides priming against A/H1N1 pandemic influenza

**Vaccines**
- **−** = PBS
- **A** = seasonal H1N1
- **F** = seasonal H1N1 + MF59
- **C** = pdm H1N1
- **C+** = pdm H1N1 + MF59

*Del Guidice et al. Science TM 2009*
*v.d.Brand et al J.Virol. 2010*
Preliminary immunogenicity results post-dose one exceed the regulatory threshold

Prior to receipt of official regents vaccines were formulated using an alternative assay for HA content. HA potencies were then retested by SRD once calibrated reagents were available.

Vaccination effectiveness studies “Swine flu 2009”

The Scottish VIPER study and a German study

- vaccination was effective
  - 97% in 15–65 age group
  - 83% in > 65 age group
- vaccination reduced risk of Influenza
- vaccination reduced risk of pneumonia and hospitalisation
- vaccination reduced mortality
In the lay press pandemic vaccines 2009 were said to be unsafe.
Europe: Experience with pandemic vaccines in mass vaccination programs

Conclusion stated by EMA

“The CHMP re-assessed the benefit-risk profile of Celvapan [Baxter], Focetria [Novartis] and Pandemrix [GSK]. Taking into account the comprehensive information available on the clinical safety and efficacy of these vaccines, the CHMP concluded that

**the benefit-risk profile of these vaccines continues to be positive.**

Consequently, the CHMP recommended the further use of the vaccines within the EU in the authorised indication even after the pandemic was declared over.”
European Medicines Agency updates on the review of Pandemrix and reports of narcolepsy (23 September 2010)

- “As per 17 September 2010, there are 81 reports from healthcare professionals suggestive of narcolepsy, all collected through spontaneous reporting systems.”

- “The European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) agreed that at present the benefit-risk balance for Pandemrix continues to be positive, and that while the review is still ongoing there was no need for Europe-wide restrictions on use.”

- “Available evidence does not confirm a link; more research needed.”

Adjuvants
for pandemic influenza vaccines

POINTS TO CONSIDER:

- effectiveness (Ag sparing, breadth/longevity response...)
- naïve versus primed individuals
- also effective and safe for seasonal vaccine usage?
- correlates of protection (HAI/VN antibody, T cells...? regulatory issues!)
- safety issues (also upon challenge; auto-immune, e.g. GBS, narcolepsy..)
- availability, IP rights, cost...
- ease to manufacture
- ease to formulate
- separate storage possible (emulsions!!)
- ...

...
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Ron Fouchier

Viroclinics Biosciences BV
James Simon
Koert Stittelaar

GSK

Novartis

Sanofi Pasteur

Solvay

Isconova

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